Seizure Pharmacology

Introduction

We are taking a big-picture approach. Antiepileptic drugs (AEDs) are antiseizure medications taken daily by patients with epilepsy to prevent future seizures. AEDs have other uses for specific diagnoses, such as subarachnoid hemorrhage, but we want you to focus on AEDs as they are used to treat epilepsy. We will also discuss medications that can abort status epilepticus seizures.

The Synaptic Cleft, GABA, and Glutamate

Just as you learned in General Physiology #8: *Synapses*, the synaptic cleft works the same way for both GABA inhibitory neurons and glutamate excitatory neurons. An action potential is carried down the axon via voltage-gated sodium channels and the nodes of Ranvier. The action potential reaches the axon terminal, where the depolarization leads to voltage-gated calcium release. Calcium enters the cell, where preformed vesicles await. With exposure to calcium, they fuse with the plasma membrane, and the neurotransmitter is released. The neurotransmitter diffuses across the synaptic cleft and binds to its receptor.

Just as you learned in *GABA Receptors and Alcohol*, GABA and glutamate have opposing effects on the postsynaptic cell. GABA binds $GABA_A$ receptors, inducing a conformational change and allowing chloride to flow into the postsynaptic cell, creating an inhibitory postsynaptic potential. Glutamate binds to both AMPA and NMDA receptors, inducing a conformational change and allowing cations (AMPA conducts Ca^{2+}, NMDA conducts Ca^{2+}, Na^+, and K^+) to flow into the postsynaptic cell, creating an excitatory postsynaptic potential.

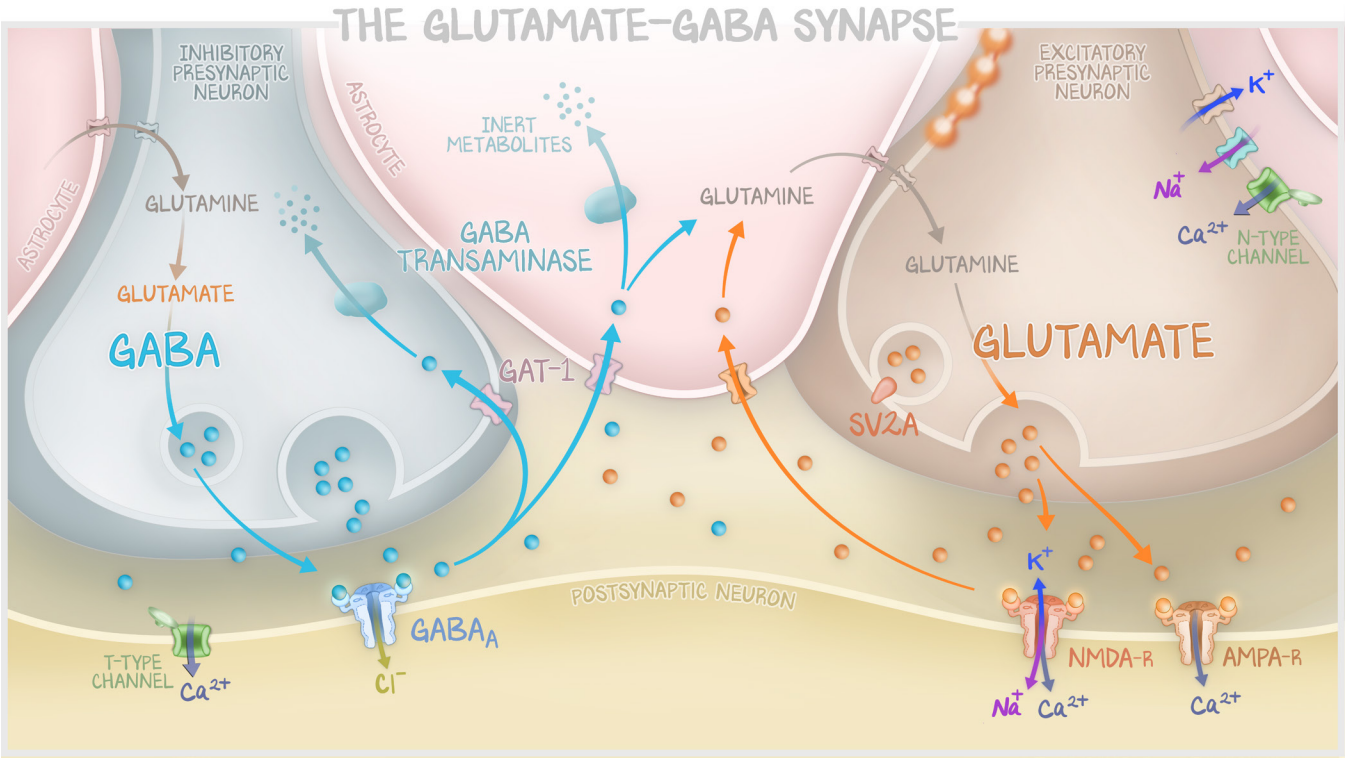

Figure 4.1: The Glutamate GABA Synapse
Make sure you are comfortable with this landscape and system. Follow the arrows, and see the potential targets. Treating seizures is about reducing the stimulatory signal (glutamate) and increasing the inhibitory signal (GABA). Everything can be a target, and many drug classes exist. Only a few are actually used. We'll cover that in the following pages.

GABA is taken up into astrocytes and the presynaptic cell by GAT-1. Within both cell types, GABA can potentially be converted into an inactive metabolite by the enzyme GABA transaminase (GABA-T). Glutamate is taken up by the neuron and astrocytes, where it is turned back into glutamine. Glutamine is the source of both GABA in the inhibitory axon and glutamate in the excitatory axon. This is meant as a review and a preview, the map for the rest of the lesson.

Using That Model to Build Antiepileptic Drug Mechanisms

We present an arbitrary categorization of antiepileptic drugs. There are so many potential mechanisms that it is extremely difficult to merely list them. So, we want you to understand four categories: glutamate exocytosis inhibitors, glutamate receptor antagonists, GABA metabolism inhibitors, and $GABA_A$ agonists. We've already covered $GABA_A$ agonists—benzos and barbiturates—and said that phenobarbital can be used for seizures (but shouldn't be) and that benzodiazepines are used to treat acute seizures, not epilepsy.

The **glutamate-releasing** excitatory presynaptic neurons have a **different** voltage-gated sodium channel and voltage-gated calcium channel than the GABA-releasing inhibitory presynaptic neurons. They do the same thing—open and allow sodium or calcium into the cell. But there are structural differences that pharmaceuticals have taken advantage of that enable medications to target glutamate neuron channels while leaving GABA neuron channels unaffected. Thus, there are **Na^+ channel blockers** and **Ca^{2+} channel blockers** that are used to reduce glutamate release and quiet a seizure. The exocytosis of glutamate relies on a transmembrane protein, SV2A. **The inhibition of SV2A** is another mechanism to reduce the glutamate signal. The inhibition of voltage-gated sodium channels limits the voltage of each action potential and makes it less likely for voltage-gated Ca^{2+} channels to open. With less calcium, less fusion and exocytosis will occur. The inhibition of SV2A would prevent the exocytosis of those vesicles, even in the presence of calcium. Thus we have categorized the medications that impact these three events as "**exocytosis inhibitors**." There is also a potassium channel agonist that serves the same purpose (ezogabine in the US, retigabine everywhere else) - reduces the frequency of calcium channels' opening by hyperpolarizing the presynaptic neuron, but it isn't used in the US, so we exclude it from our model).

At the glutamate receptor level, direct antagonism—**inhibition of AMPA or NDMA** receptors—would result in less stimulation, tipping the system in favor of GABA. Thus, we have categorized the AEDs that impact the remaining receptors as "**glutamate receptor inhibitors**." No medications target glutamine reuptake.

GABA metabolism involves uptake (GAT-1) and metabolism (GABA-T). Blocking the degradation of GABA by astrocytes and presynaptic GABA axons or blocking its reuptake from the synaptic cleft would increase the availability of GABA in the synaptic cleft. Therefore, the GABA signal would be stronger and last longer. Blocking the reuptake of GABA is achieved by the **inhibition of GAT-1**. Preventing its degradation is achieved by the **inhibition of GABA transaminase**. We have categorized these as "**GABA metabolism inhibitors**."

At the $GABA_A$ receptor level, **stimulation of GABA** (as we saw with benzos, barbiturates, and alcohol) would increase the inhibition of the postsynaptic neuron. Because we don't want you to think of benzos and barbiturates as antiepileptics but as drugs used only in the acute situation of status epilepticus, we remove them from this discussion.

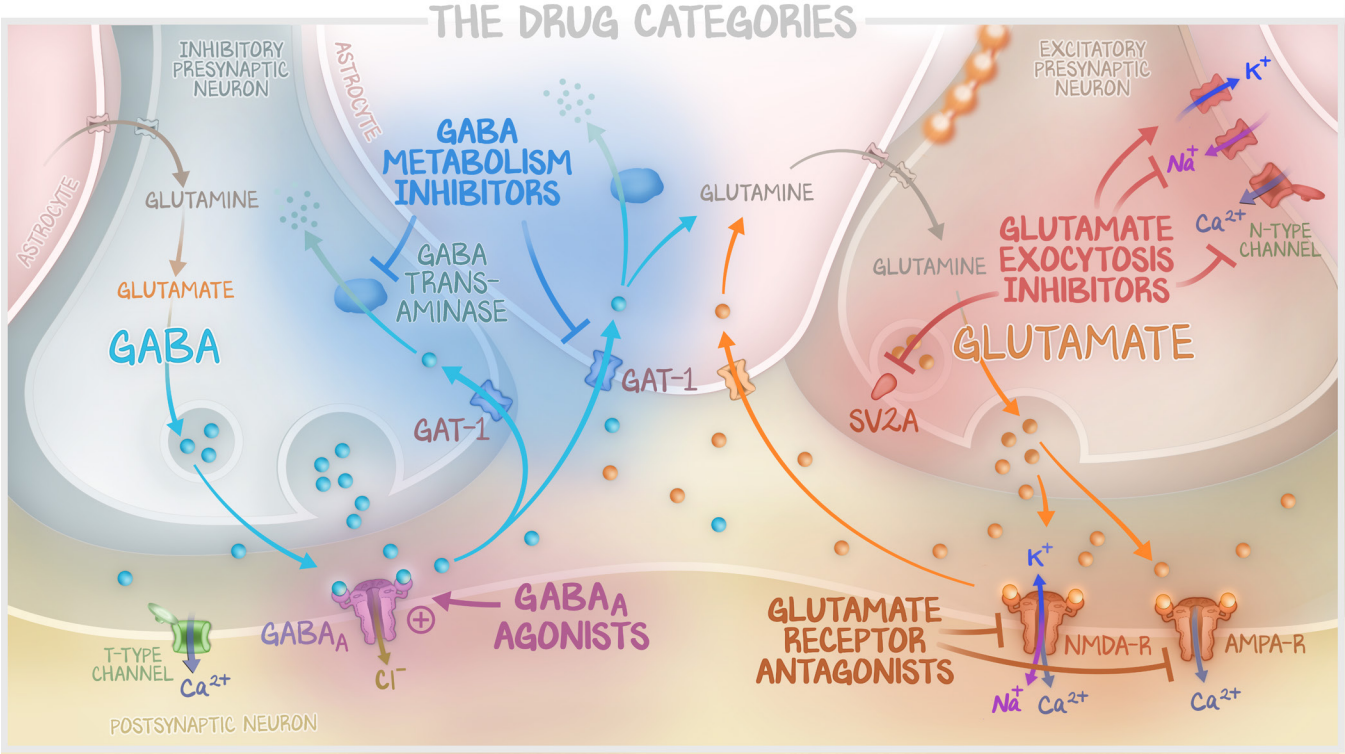

Figure 4.2: The Glutamate GABA Synapse with Drug Categories
This is to prepare you for the sheer volume of drugs that can be used to treat epilepsy and seizure disorders. There are four general categories, two each for GABA and glutamate. To reduce glutamate, drugs can prevent the exocytosis of glutamate vesicles (presynaptic) or block glutamate receptors (postsynaptic). To increase GABA, drugs can activate GABA receptors (postsynaptic) or prevent GABA reuptake and metabolism (presynaptic).

Antiepileptic Treatment

You won't have to choose escalation of therapy unless you become a neurologist. What you should know about AEDs are which ones are better **monotherapies**, the circumstances in which one is better than another, and which should be avoided based on comorbidities. Many are practically interchangeable, but at the level of the basic sciences, the goal is to get a good understanding of which AED treats which primary diagnosis. There is only a handful of first choices, and those are the drugs to know best. The rest, which are used as **adjunct therapy**, you need to know less about, focusing on their side effects. Knowing what NOT to give becomes more important than knowing what to give. So we start with a discussion of monotherapies and their indications.

There are older drugs and newer drugs. None has been shown to be better than the others, but some have been shown to do far less harm—usually the newer ones. When it comes to monotherapy, you will use levetiracetam, lamotrigine, and valproate. The only reason to prescribe anything else is that the patient needs a second AED (not something you will have to decide) or has a specific condition that necessitates it.

We are not talking about juvenile diseases like infantile spasm, or the congenital syndromes like Lennox-Gastaut. We're talking about adults with either focal or generalized epilepsy, with special considerations for women of childbearing age (WOCBA) and the elderly. We present two frameworks: one clinical, one basic sciences. The toughest part of seizure pharmacology isn't just that there are so many classes; it's also that the naming of the drugs in each class lacks a recognizable pattern. So you end up learning specific drugs, not just drug classes. In an attempt to harness spatial orientation to facilitate

memory, we have organized the medications in the following tables, either near or far from each other, then also oriented them in their own row across tables. Then we also highlight which can be learned and which should be learned (those that are in use in the United States).

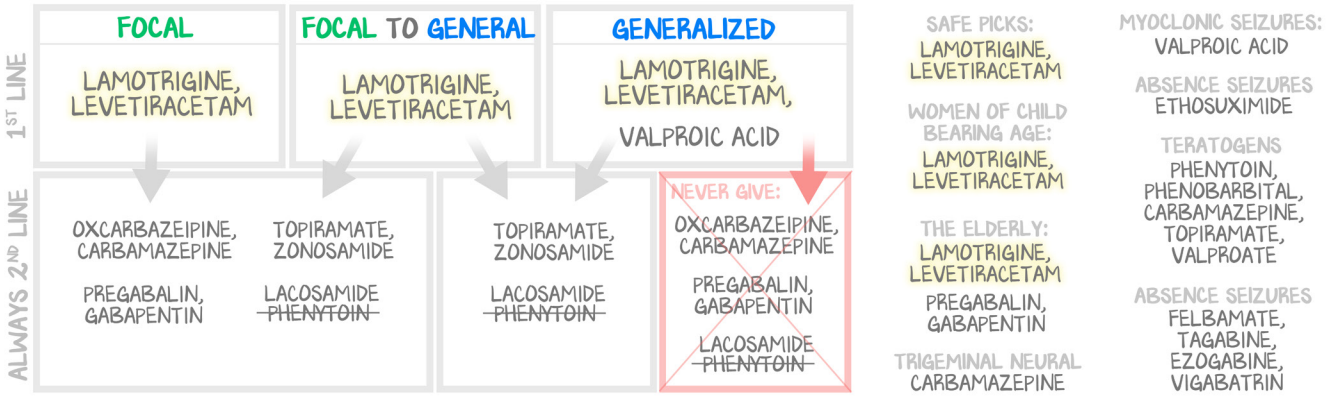

Figure 4.3: Clinical Framework
Lamotrigine and levetiracetam are appropriate for focal-to-generalized (formerly "secondarily generalized") and generalized seizures. Valproate is appropriate for generalized and myoclonic seizures. Everything else takes a back seat to those three, except under certain circumstances. Carbamazepine is used for trigeminal neuralgia, and ethosuximide is used for absence seizures. Then, the second-line agents are grouped together. Oxcarbazepine = carbamazepine (except as a teratogen and used for trigeminal neuralgia). Pregabalin and gabapentin have the same mechanism of action. We've arranged the table to show you that oxcar-carba and pregabalin-gabapentin are harmful in generalized seizures, and topiramate and zonisamide are along for the ride. Phenytoin is useful in focal, focal-to-generalized, and generalized seizures, but it has such an awful side effect profile that you should consider it only as a second- or third-line agent.

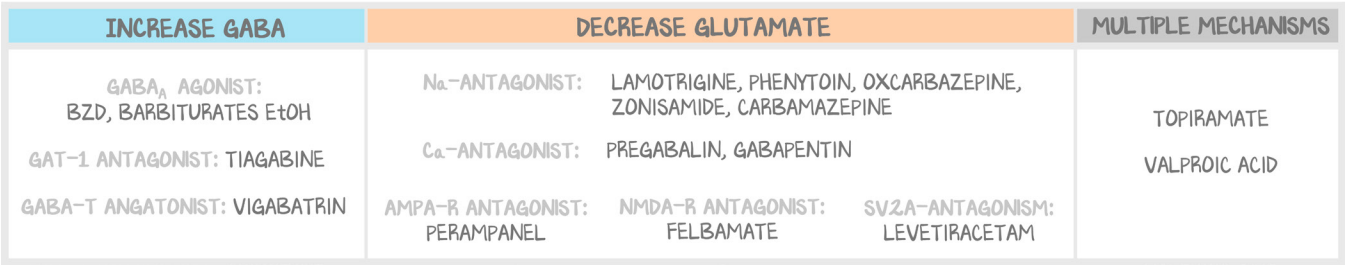

Figure 4.4: Mechanism Framework
There are two overarching mechanisms to quell activity in the CNS: increasing GABA or decreasing glutamate. Very few medication classes exist on the increased GABA side. Benzos and barbiturates can be used to stop a seizure, but aren't used for chronic management. The GAT-1 antagonist, tiagabine, and the GABA-T antagonist, vigabatrin, are only adjunct therapies, and, beyond their mechanism, you need not know anything about them. Exocytosis antagonists either impair the action potential (Na^+ channel antagonists), impair calcium influx (Ca^{2+} channel antagonists), or impair fusion and exocytosis by interacting with exocytosis proteins. All of the routinely used medications are of this class (including topiramate and valproate, which have multiple mechanisms of action). Like the GABA metabolism inhibitors, the glutamate receptor antagonists, perampanel for AMPA and felbamate for NMDA, are adjunct therapies, never first-line, and so, beyond their mechanism, there isn't too much to know about them.

Special Considerations When Choosing AEDs

Specific diagnosis. Linking a specific condition to a specific drug is crucial for licensing exams. You must memorize these. There is no other way around it. If you see the condition, pick the medication that is associated with it. **Absence** seizures are treated with **ethosuximide**. Like valproate (below), its mechanism of action is to inhibit T-type calcium channels. If ethosuximide isn't an option, choose valproate, the only other inhibitor of T-type calcium channels. **Myoclonic seizures** are also treated with **valproate** as a first line. **Trigeminal neuralgia** (a "seizure of a peripheral nerve"), a pain syndrome that involves electric shock sensation to the face, is treated with **carbamazepine**.

P450. Among the AEDs, there are P450 inhibitors (**valproate**), and there are P450 inducers (phenytoin, phenobarbital, oxcarb=carboxy). Inhibitors will result in a medication reaching toxic levels at what was once a stable dose (classically warfarin, presenting with an elevated INR or bleeding). Inducers will result in failure of a medication, such as antibiotics not combatting an infection, or oral contraceptives becoming ineffective and a woman becoming pregnant despite adherence to her regimen.

Teratogens. Avoid these AEDs in WOCBA. **Phenytoin**, phenobarbital, topiramate, valproate, and carbamazepine (oxcarbazepine is okay, but don't use it if you can use something else).

Comorbidities. You are not to memorize these. There are very good reasons to use the "second-line agents" first. But this subject is already too cumbersome, and unless you become a neurologist, these aren't decisions you will be making. Migraine relief: zonisamide, valproate, topiramate. Mood stabilization: valproate, lamotrigine, carbamazepine. Neuropathic pain relief: pregabalin, gabapentin. Weight loss: topiramate, zonisamide.

Newer vs. Older Generations, Narrow vs. Broad Spectrum

Older seizure medications tend to have more side effects than the newer, second-generation medications. The new medications are replacing the old ones. While none of the new ones has been shown to be more effective than any of the old ones, the older medications have more side effects. So what we get out of most studies is a recommendation to use one over another, with no statistically significant data demonstrating superiority. What happens is variable—should you use the drug you've always used because you can anticipate its consequences, or learn the new drugs that you aren't familiar with? Both are appropriate practice patterns. We are going to steer you in the direction of new and safe, but the vehemence with which we do that should not imply that a provider who does something different is wrong.

Narrow-spectrum AEDs are used to treat focal seizures. They include lacosamide, pregabalin-gabapentin, carbamazepine-oxcarbazepine, phenytoin, and vigabatrin. They can also be used as adjuncts to monotherapy. Broad-spectrum AEDs are used to treat generalized seizures. They include levetiracetam, lamotrigine, zonisamide, topiramate, valproate, perampanel, and retigabine (ezogabine in the United States).

Notice nothing was bolded. These are ways of classifying seizure pharmaceuticals. They aren't helpful to you.

The Exocytosis Inhibitors #1: Levetiracetam and SV2A

Levetiracetam is obviously the best antiepileptic medication. The drug is uniquely metabolized, **independently** of the hepatic P450 system—neither inhibiting nor inducing it—and, therefore, **avoiding** drug-drug interactions. Levetiracetam does NOT necessitate a prolonged titration period like other drugs because it **does NOT cause a rash, Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN)**. Levetiracetam CAN be monitored with blood levels to assess compliance and ensure that a therapeutic dose is achieved before discharge after an acute event. But routine blood work isn't required, because levetiracetam **does NOT cause pancytopenia, agranulocytosis, aplastic anemia,** or **liver disease**. It can be used in every setting—pediatric, adult, WOCBA, and the elderly—and in every type of seizure except absence—focal, focal-to-generalized, generalized. Levetiracetam is NOT better at preventing the next seizure than the older medications, but it has **none of the side effects**, requires **no bloodwork monitoring**, and is always a good first-line choice for monotherapy. Its only drawback **was** that it was new and under patent, so it **was expensive**. But now, it's generic. It's still not as cheap as phenytoin or phenobarbital, but you are training during a transition. In 2009, lamotrigine, levetiracetam, and valproate were hands-down the preferred initial agents by neurologists surveyed (except for

specific indications). Other than for potential benefits in off-label use (such as topiramate for migraine prophylaxis or carbamazepine for mood stabilization), there is no reason anyone needs to be on a dirty drug unless that person requires a second agent.

No agent has been shown to be more effective than another, but one has shown itself to be safer. As you can probably deduce, because we started with levetiracetam and told you what the side effects were NOT, those side effects are likely going to be abundant in the medications that follow. The **one thing** you should look out for is **depression**. Levetiracetam **increases the risk of suicide in those with depression**. Avoid the use of levetiracetam in patients with major depressive disorder, depressive symptoms, or any psychiatric disorder that involves the possibility of depression. After telling you how awesome levetiracetam is, this dwelling upon the condition it is harmful in—depression—was intentional.

Levetiracetam's mechanism of action is to bind to the exocytosis docking protein **SV2A.** Levetiracetam binds SV2A from the outside, from the synaptic cleft, as it is exposed to the brain extracellular fluid (bECF) during exocytosis. Levetiracetam binds to SV2A and goes along for the ride as the plasma membrane is recycled through endocytosis. SV2A is a transmembrane protein. It is required for vesicular fusion and exocytosis. SV2A isn't used in the endocytosis of the plasma membrane, vesicle formation, or filling up the vesicle with neurotransmitter. It is used only for exocytosis. Therefore both SV2A and the levetiracetam bound to it go along for the ride. And, when SV2A is given the signal to dock, the levetiracetam has bound it so it cannot. When the vesicle goes to exocytose, it cannot dock and fusion cannot occur, so no exocytosis occurs. The result is less glutamate in the synaptic cleft.

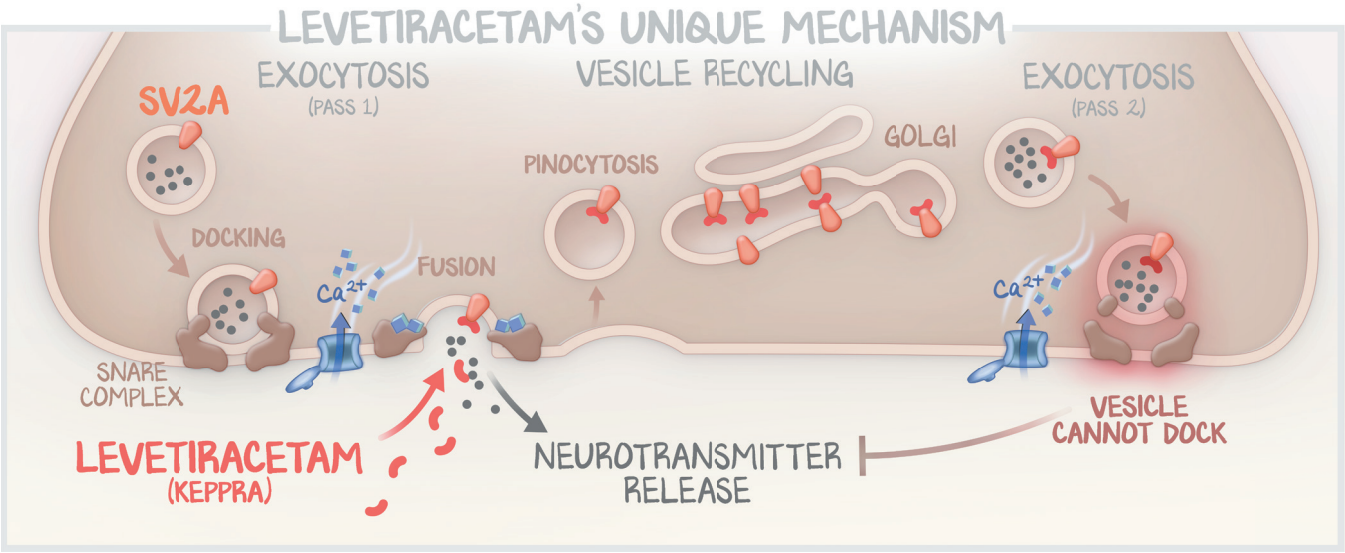

Figure 4.5: Levetiracetam's Unique Mechanism
Levetiracetam binds to SV2A as a vesicle is exocytosed. SV2A is used only in the docking and final fusion of exocytosis. Levetiracetam just hangs on to SV2A and is endocytosed alongside SV2A, so it is now within the endosome. The endosome is then loaded with glutamate. The presynaptic neuron doesn't even know of levetiracetam's presence as metabolism, synthesis, degradation, etc. all occur outside of the vesicle. But then, when the cell tries to dock and release that vesicle through fusion and exocytosis, SV2A doesn't work—levetiracetam won't let it.

The one, and quite serious, side effect of levetiracetam is suicidal ideation. Regardless, it has vastly displaced most other older mediations as a first-line agent.

The Exocytosis Inhibitors #2: Lamotrigine and Sodium Channels

Lamotrigine blocks voltage-gated sodium channels. This is an alternative to valproate (below) for myoclonic seizures if toxicity develops. Much like levetiracetam, lamotrigine is used in generalized seizures and focal-to-generalized seizures. However, it has a worse side effect profile than that of levetiracetam, being one of the drugs that **can cause SJS/TEN**. It thus requires a gradual titration. Lamotrigine is only chosen over levetiracetam when a **mood stabilizer** is needed (the patient has both bipolar disorder and seizures) or when a patient has depression.

The inhibition of voltage-gated sodium channels prevents propagation of the action potential, ensuring that fewer voltage-gated calcium channels open and, therefore, fewer vesicles fuse, resulting in less exocytosis and less glutamate activation.

Conveniently, and quite coincidentally, levetiracetam and lamotrigine both start with the letter L (see top of Figure 4.3). They are appropriate for all types of generalized seizures and safe for WOCBA and the elderly.

The Exocytosis Inhibitors # 3: Carbamazepine-Oxcarbazepine and Sodium Channels

Carbamazepine is one of the older drugs and consequently has many side effects, requires routine bloodwork, and carries a risk for SJS/TENS. Its mechanism of action is to bind and inhibit the **voltage-gated sodium channels** conducting the action potential of the presynaptic neuron. It, like many of the drugs that have this mechanism, **decreases glutamate** signaling by **inhibiting exocytosis**.

Carbamazepine has one of the highest risks for **SJS/TEN**, especially in patients of Asian descent. So much so that screening for **HLA-B*1502** in patients of Asian ancestry is mandatory before starting the drug. Simple avoidance of the drug is preferred.

Carbamazepine has a host of side effects and is a teratogen. It can lead to **agranulocytosis** and **aplastic anemia**, so routine CBCs are required while on therapy. It has a high risk of **hepatotoxicity** and requires routine LFTs. It is one of the medications (and the only AED) that cause **SIADH**, presenting with hyponatremia. Thus, routine BMPs are required. This effect is amplified in the elderly. It is an **inducer** of cytochrome P450 and causes many drug-drug interactions. It is one of the **teratogenic AEDs** that leads to **cleft lip/palate** and **spina bifida**. WOCBA should not be exposed to carbamazepine, especially when other options exist.

It is only used for **focal seizures** (focal and focal-to-generalized), and only as a **second-line agent**. The only time this medication is chosen first-line is if the patient has **trigeminal neuralgia**; otherwise, its toxicity and limited scope render it one of the old, historical medications, and not one regularly used.

For most intents and purposes, carbamazepine is oxcarbazepine. The exceptions are that oxcarbazepine isn't a teratogen, and doesn't treat trigeminal neuralgia.

The Exocytosis Inhibitors #4: Phenytoin and Sodium Channels

An ancient drug, phenytoin used to be the best we had. It works—seizures are prevented—but at an enormous cost. And it isn't as if that cost makes it better at preventing seizures, trading safety for potency. Phenytoin is just as good at preventing seizures as other medications. So, the positive is just as positive. But the immense side effect profile and drug-drug interactions make the benefit not worth the cost. The negative is so much more negative than that of any other agent, it should never be used as monotherapy, and it should only be used as an adjunct to monotherapy. With newer medications, particularly **lacosamide**, which has the same mechanism of action and the same indications, but none of

the side effects and may be better at reducing seizures (sort of, since there isn't great data), phenytoin is disappearing from the world of seizure treatment.

It, like lamotrigine and carbamazepine, **blocks voltage-gated sodium channels**. It is useful for focal-to-generalized and generalized seizures. It is not indicated for absence seizures.

Begin the tale of how awful a drug it is. It is a **potent inducer** of CYP-450, most famously (on licensing exams) causing reduced effectiveness of oral contraceptives and warfarin. It, like ethanol, has **zero-order kinetics**. The liver's ability to process phenytoin is completely saturated, which means that it lingers in the system, and toxic levels easily accumulate.

The side effects can be recalled by the mnemonic PHENYTOIN: **P**450 induction, **H**irsutism, **E**nlarged gums (a fudge on gingival hyperplasia), **N**ystagmus, **Y**ellow-brown skin (to make the mnemonic work), **T**eratogenicity (fetal hydantoin syndrome), **O**steopenia, **I**nhibited folate absorption (leading to macrocytic megaloblastic anemia), and **N**europathy. It is also one of the rash-inducing drugs (early, old, dangerous) that can lead to **SJS/TEN**.

The teratogenicity is severe. It causes microcephaly, midfacial hypoplasia, cleft lip/palate, finger and nail hypoplasia, and hirsutism.

Don't use phenytoin unless you are really sure that it is the right move. As in, medical science develops a seizure sensitivity test that assesses for how sensitive a person's epilepsy is and phenytoin is the only AED that a person's epilepsy is sensitive to. This test is obviously not feasible. This paragraph is to reinforce the fact that **phenytoin's side effect profile makes it often appear on licensing exams, and it should not be used in real humans**.

The Exocytosis Inhibitors #6: Pregabalin-Gabapentin and Calcium Channels

Pregabalin and gabapentin have similar profiles and mechanisms of action, and so are discussed together, in the same manner as carbamazepine and oxcarbazepine. They both bind and **inhibit N-type voltage-gated calcium channels**. These channels open in response to a depolarization action potential and permit calcium entry into the cell. Calcium is the signal by which the vesicles dock and undergo exocytosis, and therefore these drugs inhibit glutamate release.

These drugs are used more often in the treatment of **peripheral neuropathy**, a neuropathic pain disorder where the nerves send pain stimuli when no structural lesion is present. They do help with seizures, but are **very sedative** (more so than the others) and can lead to ataxia. **Gabapentin** is recommended as an alternative to lamotrigine and levetiracetam in the **elderly**. This recommendation is in case there is a comorbid condition that warrants gabapentin already; it can be used as the first-line agent. Again, levetiracetam is better, but to avoid polypharmacy, gabapentin is available.

Drugs with Multiple Mechanisms #1: Topiramate (and Zonisamide)

Topiramate is one of the "broadest-spectrum AEDs" because it has multiple mechanisms of action. It blocks voltage-gated Na^+ channels, enhances GABA activity on $GABA_A$ receptors, and antagonizes NMDA receptors. So, you won't have to know its mechanism. You may notice from the clinical framework that it is in that vague "second-line" use, but also not in the one that worsens generalized seizures. It is **never the** first line and can be used interchangeably as a second-line agent for focal-to-generalized or generalized.

The side effects of topiramate are similar to those of the other AED agents. Making GABA win can cause sedation, dizziness, fatigue, and headaches. But topiramate is unique in that it causes **impaired**

cognition and expressive aphasia that may mimic a stroke. There won't be sensory or motor functions to accompany it, and topiramate will be elevated in the blood. It generally causes CNS depression, just as all AEDs do, but when it rises above therapeutic levels, cognitive dysfunction and word-finding issues will develop.

In addition, **visual disturbances** should point you to topiramate. Myopia (nearsightedness) and glaucoma can occur within therapeutic levels.

The reason to choose topiramate over another second-line agent is if the patient **also has migraines**. Topiramate is one option for migraine prophylaxis. It is not the first-line for seizure, and it is not first-line for migraines. But if someone has both, topiramate may be the treatment of choice on a licensing exam.

Zonisamide, for all intents and purposes, is topiramate. Most resources list them as essentially the same drug, with the same indications and side effects.

Drugs with Multiple Mechanisms #2: Valproate

Like topiramate, valproate (also known as valproic acid) has multiple mechanisms and is thus only appropriate for generalized or focal-to-generalized seizures. It is one of the "big three" (levetiracetam, lamotrigine, valproate) that should be your first go-to for AED. But valproate isn't as safe as lamotrigine or levetiracetam. It is absolutely **the best choice** in **myoclonic seizures**. However, it is a **teratogen** and should be avoided in **women of childbearing age**. It causes **neural tube defects** (spina bifida spectrum), and high-dose folate supplementation is required with valproate should it be necessary for a WOCBA. It is older but also well known.

Its mechanisms of action are to inhibit **voltage-gated sodium channels** and block **T-type calcium** channels (like ethosuximide, not the N-type calcium channels at the ends of synapses nor the L-type calcium channels found in the heart), and it also affects GABA metabolism, increasing GABA concentrations in a way that is not fully elucidated (likely GAT-1 inhibition, but medical science isn't sure).

It is the **only AED to inhibit P450**. Because it is also metabolized by P450, it is thus metabolized in the liver. It should be **avoided in liver disease**. This is the lesser of the "big three" because **pancreatitis** and **hepatotoxicity** necessitate routine lab work—**LFTs**. Lamotrigine and levetiracetam do not. So although valproate is a good antiepileptic medication, its inconvenience and possible side effect profile relegate it to first-line treatment for myoclonic seizures only.

Some That Didn't Get Mentioned

Ezogabine (in the US, retigabine everywhere else) opens presynaptic potassium channels, hyperpolarizing the presynaptic cell, preventing the exocytosis of glutamates

Lacosamide is the better phenytoin. It blocks voltage-gated sodium channels on the presynaptic cell. It can be used as a monotherapy for focal seizures. It is safe in the pediatric population, four years and older.

Vigabatrin is an inhibitor of GABA-T. It is used for focal seizures—monotherapy or adjunct—in the pediatric population.

Felbamate is an NMDA antagonist. It is still available for use, but only on a case-by-case basis. It causes agranulocytosis and hepatotoxicity such that, although not banned, for all intents and purposes, it is banned. It is so unsafe that you should never see the name outside of schooling.

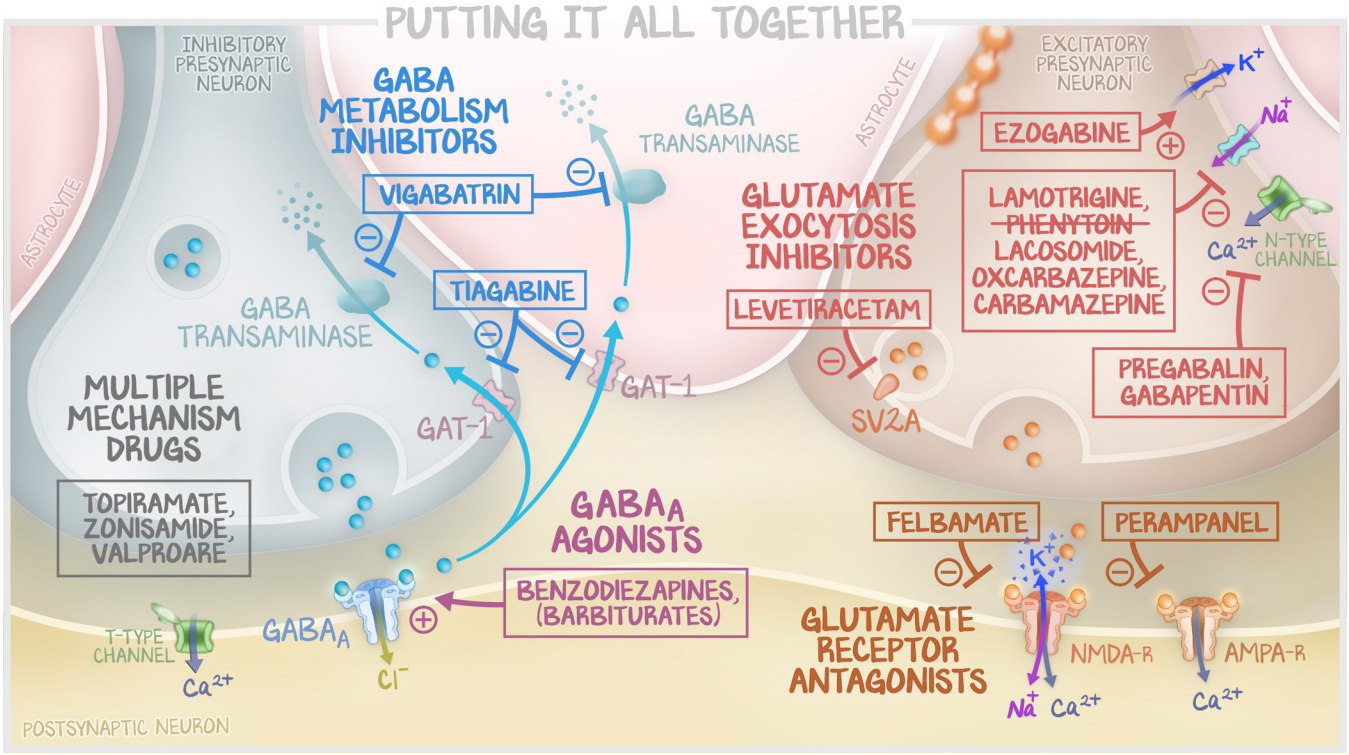

Figure 4.6: Putting It All Together
We chose to leave rarely used medications, such as vigabatrin, tiagabine, retigabine, felbamate, and perampanel, out of the discussion. We also excluded most of the alternative derivative medications of each drug. There are so many AEDs that trying to get through them all is a futile task. We want you to know that there are more than are presented here, but we felt this was enough.

Treatment of Status Epilepticus

Goal 1: **Break the seizure.** This is done with **benzos**. Specifically, intravenous **lorazepam**. You give lorazepam, you give more lorazepam, you give more lorazepam, you start the AED of choice (next), and you give more lorazepam. If ongoing seizure activity is seen after two doses of lorazepam, paralysis and intubation should be considered. You give more lorazepam while the AED of choice is started. How much lorazepam is in one dose? It isn't specified. The idea is that you keep giving more until they stop seizing.

Goal 2: **Prevent the next seizure.** Traditionally, this has been taught as (fos)phenytoin IV. We're not teaching you that. **Levetiracetam** is just as good at preventing the next seizure as phenytoin, but, as described above, can be brought up to therapeutic levels immediately and has no serious side effects. You may see (fos)phenytoin on a licensing exam, and it may be the right answer for status epilepticus. If levetiracetam is an option, pick it. Chances are, they are going home on an oral medication, and levetiracetam is the cleanest.

Goal 3: **Silence their brain.** If the lorazepam and AED of choice (levetiracetam, not phenytoin; but use phenytoin if that's all you have) haven't broken the seizure, then $GABA_A$ receptors need to be stimulated so hard that you are certain to cause respiratory depression. This is what needs to be done to break the seizure. The patient is sedated with **propofol** ($GABA_A$ stimulator), paralyzed with a paralytic (it sounds redundant here, but we'll teach you about paralytics later in Neuroscience (Clinical Cortex #8: *Pain and Analgesic Tracts*), and intubated, and then either **propofol** or **midazolam infusion** is begun. A rapid-on, rapid-off paralytic (succinylcholine) is used to monitor for seizure activity. EEG monitoring is usually started.

Status epilepticus is diagnosed after 5 minutes of a tonic-clonic seizure. Do not learn the time frames for other seizures unless your specialty demands it. Definitely not now. The protocols proposed by epileptic societies are fine and dandy, and they break things down into neat time windows. Give lorazepam once at minute 5 and repeat before minute 20. At 20 minutes of seizure activity, start the second intervention (antiepileptic of choice). At 40 minutes of seizure activity, there is no guidance. Practically, what happens is the person makes it to minute 5, and 4 mg IV lorazepam is ordered. It takes a few minutes to get it from the controlled substance locker in the ED. It is administered. The IV antiepileptic is ordered and sent from the pharmacy. The second dose of 4 mg IV lorazepam is ordered and given prior to the arrival of the AED. The AED arrives and is given. No one watches the clock. A third dose of 4 mg lorazepam is ordered. The AED finishes its bolus administration, and the patient still has seizure activity. Etomidate and succinylcholine are pulled from the crash cart, and a laryngoscope is pulled from the airway bag. A respiratory therapist wheels in the ventilator, one nurse is working the line, and another is bagging the patient with 100% oxygen. Rapid-sequence intubation is performed, and the patient is placed on a ventilator. A rapid-acting paralytic is chosen so as to monitor for epileptic contractions. Continuous EEG is ordered, and the person is started on a midazolam infusion. Things take time to happen. Someone has to go get the medication, start a line, spike a bag, and do the intubation. They have to be rolled into an elevator and brought to the ICU where a nursing handoff takes place. It is more important to break the seizure and save their brain than argue about what medication you give in Goal 3. Midazolam, pentobarbital, propofol, and thiopental are all okay.